REMARKS

The above amendments are presented in response to the Office Action dated November 21, 2005. Claims 1-19 are pending in the application. Claims 1, 5, 12, 15, and 16 have been amended. No new matter has been added.

Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim the invention to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

In light of the claim amendments and the following remarks, Applicant respectfully request that the Examiner withdraw the rejections and pass this case to issuance.

Objections to the Drawings

In response to the objection to the Drawings, Applicants submit replacement drawing sheets 2-4, 7-10, 13, 16 and 17.

Objections to the Specification

As requested in the Office Action, the specification has been amended to correctly identify trademarked reagents.

The Office Action states that there is no description of Figs 2E-2H. In response, applicant submits that as indicated on the Figures, the left panel (i.e., Figs 2A, 2C, 2E, and 2G) are different cell types that are identified using antibodies for particular markers that are present on the cell type. Fig 2A, are SIRP myeloid cells, Fig 2C are dendritic cells, Fig 2E are helper T cells/macrophages, and Fig 2G are monocytes/macrophages. The right panel (i.e., Figs 2B, 2D, 2F and 2H) are each of the different cells types that also show expression and co-localization of the NMDAR1 protein in each cell type, determined by using antibodies

against the NMDAR1 protein, as described at page 55, line 17 through page 56, line 8 of the specification.

The Office Action notes that the bars in Fig. 6H are not labeled. Applicant respectfully disagrees with this rejection since the bars are labeled in the figure. Nonetheless, Applicant has amended the specification to recite the labels identified in the figure.

The Examiner states that the Drawings in Figs. 7A-7B cannot be differentiated because both lines are solid. Applicant asserts the lines are labeled are clearly labeled in the figures. The squares-solid lines are AAVlac-treated animals, while the triangles-solid lines are AAVNMDAR1-treated animals.

The Office Action asserts that in Figs 12A-12D, it cannot be determined which lines and bars represent each particular rat group. Applicant asserts that the graphs and bars are labeled, and has also amended the specification to recite the labels identified in the figures.

Accordingly, Applicant respectfully requests that the Examiner withdraw these objections.

Objections to the Claims

In response to the Examiner's suggestion, claim 5 has been amended to correct the typographical error. The Examiner is thanked for his careful reading of the specification.

Rejection of Claims 1, 2, 5-12, and 15-19 Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1, 2, 5-12, and 15-19 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that "claims 1, 2, 5-12, and 15-19 are drawn to a neurological vaccine comprising a vector encoding *any* neuroreceptor antigen for treatment of *any* injury..." In order to expedite prosecution, Applicant has amended independent claims 1, 12 and 16 (and

claims dependent thereto) to recite "an N-methyl-D-aspartate (NMDA) antigen." Support for this amendment can be found throughout the specification as originally filed, and specifically at page 16, lines 17-18. In addition, independent claims 1, 12 and 16 (and claims dependent thereto) have been amended to recite providing "neuroprotection" to the subject. Support for this amendment can be found throughout the Specification, or specifically at page 38, lines 19-22). Accordingly, no new matter is added. The Examiner is hereby requested to withdraw this rejection in light of these amendments.

Rejection of Claims1-19 Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-19 are rejected under 35 U.S.C. § 112, first paragraph, because the specification "while being enabling for a neurological vaccine comprising an AAV vector encoding NMDAR1 and a method of ameliorating brain damage associated with epilepsy or stroke in a rat, via prior oral administration of said vaccine, does not reasonably provide enablement for a neurological vaccine comprising any vector encoding *any* neuroreceptor antigen for treatment of *any* injury, disease or excessive neuronal activity, and a method of modulating a neurological disorder in any subject" Applicant respectfully traverses this rejection.

As amended, the claims are directed to a vaccine comprising a specific antigen, *an N-methyl-D-aspartate (NMDA) antigen*, and provides a specific effect, *neuroprotection*. The expressed antigen elicits production of antibodies the systemic circulatory system of the subject. These antibodies circulate in the circulatory system until the blood-brain barrier has been compromised. Upon compromise of the blood-brain barrier, these circulating antibodies can cross the blood-brain barrier, can pass into the central nervous system of the subject, and can bind to, and modify the function of, a target receptor associated with a neurological disorder to provide a neuroprotective effect. These antibodies can either directly modify the function of the target receptor on the neuronal cell, for example, by inhibiting receptor activity, or alternatively, they can indirectly affect the function of the target receptor, for example, by altering a protein or a downstream process that is associated with the target receptor.

Applicant respectfully traverses this rejection, as the Examiner is attempting to use this rejection to limit the scope of Applicant's claims to cover only the embodiment of the invention that is disclosed in the working examples. The specification of the present invention provides adequate teaching and guidance to enable one of ordinary skill in the art to make and use the claimed invention to modify the function of a variety of target receptors associated with neurological disorders.

The working examples provided by the specification of the present invention are *merely illustrative* of the underlying inventive concept of Applicant's invention – they do *not* represent the sum total of Applicant's underlying inventive concept. An underlying inventive concept of the claimed methods involves the production of antibodies that have been raised against a central nervous system antigen circulating in the systemic circulatory system of a subject. These antibodies circulate in the circulatory system until the blood-brain barrier has been compromised. Upon compromise of the blood-brain barrier, these circulating antibodies can cross the blood-brain barrier, can pass into the central nervous system of the subject, and can bind to, and modify the function of, a target receptor associated with a neurological disorder, a neuroendocrine disorder, or cognition. These antibodies can either directly modify the function of the target receptor on the neuronal cell, for example, by inhibiting receptor activity, or alternatively, they can indirectly affect the function of the target receptor, for example, by altering a protein or a downstream process that is associated with the target receptor. Thus, the NDMAR1 working examples provided in Applicant's specification simply represent *one* embodiment of this underlying concept.

Accordingly, the scope of Applicant's claimed methods should not be limited to only the NMDAR1 antigen, because Applicant has provided adequate disclosure for other suitable antigens that can be readily substituted into the methods disclosed by the present specification to generate circulating antibodies that can cross a compromised blood-brain barrier and bind to a target receptor. For example, at page 16, line 14 through page 17, line 13, Applicant has disclosed other NMDA receptor subunit families, as well as a number of references that would

direct one having ordinary skill in the art to further information regarding these NMDA receptor subunit families.

Additionally, Applicant has disclosed and provided guidance for a number of *in vivo* animal models of neurological disorders, which can be used to test the efficacy of any alternative NMDA receptor subunit antigens that are used in the claimed methods of the present invention. Likewise, Applicant has also disclosed a number of behavioral tests to determine the cognitive effects, if any, that may accompany the use of other suitable antigens or suitable target receptors in the claimed methods. In light of these disclosures, Applicant's specification clearly provides adequate guidance for testing and using additional suitable antigens and additional suitable target receptors for use in the disclosed methods of the present invention to generate antibodies that can cross a compromised blood-brain barrier and modify the function of the selected target receptor.

Applicant's claims are entitled to have a scope that cover all subject matter that is adequately enabled by the disclosure in the present specification. Here, the relative level of skill in the art is fairly sophisticated, and consequently, a person having ordinary skill in this art would be familiar with a large number of target receptors associated with neurological disorders. Accordingly, it would not constitute undue experimentation for a skilled artisan, upon reading Applicant's specification, to identify other target receptors for use in the claimed methods of the present invention. Once the skilled artisan is aware that neurological diseases and neuroendocrine disorders can be treated, or cognition can be improved, by the production of circulating antibodies that can cross a compromised blood-brain barrier, it is merely routine experimentation to run the identified target receptors through the claimed methods in order to test their efficacy in treating neurological disorders.

The claims are sufficiently enabled by the specification of the present invention to provide one of ordinary skill in the art with adequate guidance on the administration of the vaccine. The specification describes that the preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). Particularly by intramuscular or subcutaneous injection (*See* page 27, lines 11-15). the specification also describes a number of ways that the vaccine can be formulated for administration, for example

at page 26, line 22 though page 30, line 25, and more specifically at page 26, line 22 through page 27, line 24. In particular, the specification of the present application describes in detail how the presence of a central nervous system antigen can be induced in the circulatory system of a subject. As disclosed at pages 30-35, "[g]enerally, the antigen is delivered to the systemic circulatory system using methods known in the art." These methods include the direct administration of the antigen into the systemic circulatory system of a subject, such as for example, by peroral administration of the antigen or intramuscular injection of the antigen. The methods of administration disclosed by the specification also include the indirect administration of the antigen into the systemic circulatory system, such as for example, by the delivery of DNA encoding the central nervous system antigen, which can then be used to express the antigen, thereby inducing the presence of the antigen in the circulatory system of the subject. According the specification at pages 30-32 and 34-35, this DNA can be delivered to a subject in a variety of ways, such as for example, by vaccination with a viral vector construct containing an exogenous nucleic acid molecule encoding the desired antigen, by liposome delivery or by vaccination using a gene-gun-based delivery, in which the DNA can be delivered as naked DNA without an expression vector, or alternatively, the DNA can be inserted into an expression vector.

Furthermore, the specification provides ample guidance on how to make and use a DNA vaccine. For example, in terms of quantity, applicant states that the dose and effective amount can be determined based on the characteristics of the active compound and provides a non-limiting range of about 0.1-20 mg/kg, more preferably 1-10mg/kg. The skilled artisan will appreciate that these doses will vary according to the size, sex and weight of the subject (*See* page 30, lines 3-25).

As stated in MPEP 2164.02, "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." An animal model is acceptable where it is recognized in the art that this model correlates to a specific condition. If this has not yet been established in the art, the animal model is acceptable if one skilled in the art would accept the model as *reasonably correlating* to the condition.

This "reasonableness" standard serves to distinguish the enablement requirement of the patent laws from the more stringent standards of the FDA. Moreover, as the Examiner is aware, considerations made by the FDA for approving clinical trials are very different from those made by the PTO in determining whether a claim is enabled, *i.e.*, safety considerations are more properly left with the FDA. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

In the present invention, the "condition" comprises neurological disorders, such as stroke, epilepsy and learning and memory impairment. A number of art recognized animal models were used in the experiments described in the specification, such as the endothelin-1 model of middle cerebral artery occlusion (MCAO), kainic acid of epilepsy, and learning and memory tests such as the Barnes circular platform task and a contextual association task. As described in the Specification, the endothelin-1 model of middle cerebral artery occlusion (MCAO) described by Sharkey *et al.*(1995) *J. Neurosci. Methods* 60: 125) has been used previously to test novel anti-stroke drugs including the NMDA receptor antagonist, MK-801 (Sharkey *et al. Supra*, and Butcher *et al.* (1997) *J. Neurosci.* 17: 6939). The use of kainic acid to induce seizures and neuropathological changes in a subject is also a well-known and art-accepted model for evaluating treatment that can prevent seizure-induced structural damage (see, e.g., Leite et al., *Epilepsy Res* (2002) 50(1-2):93-103). Kainic acid induces changes that mimic human temporal lobe epilepsy, generalized motor seizures, as well as the pattern of cell damage caused by seizures in the hippocampus (see, e.g., Miettinen et al., *Brain Res* (1998) 813:9-17).

In example 3, Applicant has demonstrated the neuroprotective effect against epilepsy using a well established and art recognized animal model for epilepsy. In these experiments, rats were vaccinated with a gene encoding an NMDAR1 antigen. Circulating antibodies were produced in the circulatory system of these animals soon after vaccination. The presence of these antibodies was detected in the blood at 4 weeks post vaccination, and continued to remain in the circulation for at least 4 months afterwards (*See* Figure 3B, lanes 3 and 4, respectively).

Applicant demonstrated the neuroprotective effect of these circulating antibodies by inducing epileptic seizures in these animals. In Example 3, Applicant shows that the circulating antibodies were able to cross the blood-brain barrier that was compromised by the kainate-induced seizures. After crossing the blood-brain barrier, the antibodies were able to bind to the target receptor on the neuronal cell, in the central nervous system of the animal *i.e.,* the NMDA receptor, and modify the function of the target receptor to protect the animal from having seizures. Fig. 4A clearly shows no signs of electrographic seizure activity in animals with antibodies against NMDAR1, demonstrating the neuroprotective effects of the circulating antibodies. In contrast, control animals vaccinated with AAVlac, were not protected and developed seizures within 10 minutes of kainate drug administration.

The neuroprotective effect was not only measured by outward appearance of the animals, *i.e.*, seizures, but also by isolating the brains of these animals and using immunochemistry techniques. Neuronal death typically occurs as a result of seizures. The results showed that neuronal death in the hippocampus only occurred in animals that were not treated with the neuroprotective vaccine. In contrast, those animals which had previously been vaccinated, and did not have seizures, were protected and did not display signs of hippocampal injury (*See* Example 3, page 59, and at page 3, lines 2-7).

Applicant also demonstrates the anti-stroke and ischemic neuroprotection efficacy of the neuroprotective vaccine using an art recognized animal model for stroke (*See* Example 4, at page 64). Animals with circulating antibodies displayed a much reduced total infarct volume in the ipsilateral stratium and/or cortical regions (approx. $19.2+6.2$ mm^3) compared to those animals that were not treated (approx. $66.4 +12.4mm^3$).

Applicant further demonstrates that the neuroprotective effect of the neuroprotective vaccine can occur either by directly modifying the function of the target receptor, or by modifying the function of a downstream process that involves the target receptor *i.e.,* indirect modification.

Applicant demonstrates the neuroprotection effect of the vaccine resulting from direct modification of the NMDA receptor using fluorescent calcium loading techniques (*See* Example 6, at page 66). To demonstrate this direct modification of the NMDA receptor on a neuronal cell, circulating IgG antibodies produced in rats vaccinated with the neuroprotective vaccine were isolated. These isolated IgG antibodies were incubated *in vitro* with cultured primary neuronal cells which express the NMDA receptor. The cultured neuronal cells treated with the isolated IgG antibodies did not display an increase in fluorescent signal compared with control cells (cultured neuronal cells treated with the IgG antibodies isolated from animals treated with AAVlac as a positive control). These results show that the IgG antibodies isolated from the NMDAR1 vaccinated animals bind to the NMDA receptor expressed in cultured neuronal cells, and blocks the increase in calcium uptake by these NMDA receptors. This demonstrates the *direct* modification of the NMDA receptors by the IgG antibodies. In contrast, there was an increase in the calcium signal in untreated cultured neuronal cells, or those treated with IgG antibodies isolated from animals treated with AAVlac because there were no NMDA antibodies to block calcium uptake by the NMDA receptors.

As a result of the circulating antibodies binding to a target receptor and modifying its function, downstream processes that involve the target receptor may also modified, *i.e.,* indirect modification. To demonstrate that the circulating antibodies can *indirectly* effect processes associated with the NMDA receptor, Applicant investigated the expression of the Krox-24 protein, a protein typically activated by the NMDA receptor (*See* page 70, line 8 through page 71, line 12). The results show that the levels of Krox-24 protein were significantly reduced within the cortical brain regions of animals treated with the NMDA neuroprotective vaccine (*See* Fig. 10 C). This data shows that the circulating antibodies not only *directly* modify the NMDA receptor by binding to it, but also *indirectly* modify other processes or proteins involved with the NMDA receptor.

Applicant has also demonstrated the improvement in cognition using the neuroprotective vaccine. In Example 7, Applicant describes the effect of the NMDA vaccine on learning and memory by performing a series of behavioral tests on the vaccinated animals.

The results from the various behavioral test demonstrated that the vaccinated animals showed a significantly improved performance, for example in the Barnes maze test (page 74, lines 3-6), and had improved contextual memory in the freezing response test (page 74, lines 11-20).

Accordingly, the animal models of the Specification are art-recognized and used for correlating neurological disorders in humans. The animal models are used successfully in the instant application and are recognized by one skilled in the art as *reasonably* correlating to the conditions, as required by MPEP 2164.02.

Thus, in view of the knowledge available in the art and with the guidance provided by applicant in the specification, a skilled artisan would be able to make and use the claimed invention without undue experimentation. For all of these foregoing reasons, Applicant respectfully requests that the Examiner withdraw all rejections under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-19 Under 35 U.S.C. §112 Second Paragraph

Claims 1-19 have been rejected under 35 U.S.C. § 112, second paragraph as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

Claim 1 has been amended to delete the phrase "excessive neuronal activity" thereby rendering the rejection moot.

Claims 2, 5, 6, 11 and 15-19 are rejected since they are drawn to any "neurological disorder" and the metes and bounds of the claims cannot be determined. Applicant respectfully disagrees and directs the Examiner to page 38, lines 23 through page 39, line 2, where the metes and bounds of the term "neurological disorders" is clearly defined:

> "Neurological disorders to be treated by the invention include, but are not limited to, epilepsy, stroke, Parkinson's disease, Alzheimer's and other disorders in which the disease process is in part mediated by a brain protein or where a molecule binding to a brain protein would alter the disease phenotype,

> for example proteins involved in the signal transduction of neurotransmitters including receptors and ion channels, or the synthesis of neurotransmitters or the uptake and transport of brain chemicals. Representative examples of neurotransmitter receptors include, but are not limited to, the NMDA, AMPA and kainate receptors, dopamine, serotonin and noradrenergic receptors and transporters and neuropeptide receptors including the neurokinin-1 (NK1) receptor."

Claim 12 has been amended to replace the term "neurological condition" with "neurological disorder" thereby rendering this rejection moot.

In light of the amendment to claim 12, the lack of antecendent basis in claims 15 has been corrected.

Claim 15 has been amended to correct the clerical error pointed out by the Examiner.

In light of these amendments, the Examiner is hereby requested to withdraw the indefiniteness rejections.

Rejection of Claims 1-8, 10, 16-19 Under 35 U.S.C. §102

Claims 1-8, 10, 16-19 have been rejected under 35 U.S.C. § 102, as having been anticipated by Lissin *et al.* (PNAS 95: 7097-7102 (1998)). In particular, the Examiner has asserts that:

> ...the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art...Lissin et al. provides guidance on an adenovirus that encodes an NMDA receptor (NR1), which is capable of being expressed in cultured hippocampal neurons....

Applicant respectfully traverses this rejection. Lissin et al. simply describes a reagent that can be used in *in vitro* cell cultures to determine localization to synapses. There is no suggestion or even a reason to assume that the HA tagged NR1 described by Lissin et al. can be expressed *in vivo*, "such that the expressed antigen elicits production of antibodies in a

circulatory system of the subject, wherein the antibodies pass across a blood-brain barrier into a central nervous system upon injury." Since each and every element of the claimed invention is not taught by the Lissin reference, the Examiner is respectfully requested to withdraw the novelty rejections.

CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. The Examiner is urged to telephone the undersigned Attorney for Applicant in the event that such communication is deemed to expedite prosecution of this matter.

Dated: May 22, 2006

Respectfully submitted,

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